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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,695	KUMAZAWA ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,30,32,34,36,38,40,42,44,46,48,50,52 and 54-59* is/are pending in the application.

4a) Of the above claim(s) *28,44,46 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32,34,36,38,40,42,50,52 and 54-59* is/are rejected.

7)☒ Claim(s) *30,32,34,36,38,40,42,50,52,54 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *24 April 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 24 April 2009 in which claims 1-27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 and 53 were cancelled, claims 30, 32, 34, 50 and 54-56 are amended to change the scope and breadth of the claims, claims 36 and 42 are amended to correct grammatical and typographical issues, and new claims 57-59 are added.

Claims 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52 and 54-59 are pending in the instant application.

Claims 28, 44, 46 and 48 were previously withdrawn from further consideration in the Office Action dated 24 October 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

New claims 57-59 are drawn to the elected invention.

Claims 30, 32, 34, 36, 38, 40, 42, 50, 52 and 54-59 are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/JP05/03234 filed on 21 February 2005 and claims priority to Japan foreign application 2004-043481 filed on 19 February 2004. A certified copy of the foreign priority document in Japanese has been received. It is acknowledged that Applicants filed an English translation of the foreign priority document on 24 April 2009. However, Applicants are requested to note that the

claim to foreign priority has not been perfected because a statement indicating that the translation of the certified priority document is accurate was not filed together with the translation of the certified document. See CFR § 1.55(a).

Information Disclosure Statement

The information disclosure statement (IDS) dated 24 April 2009 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Rejections Withdrawn

Applicant's amendment, filed 24 April 2009, with respect to the rejection of claim 54 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, has been fully considered and is persuasive because the claim as amended explicitly recites "nitric monoxide" instead of "NO," thereby permitting a skilled artisan to ascertain the metes and bounds of the Applicant's invention.

Applicant's amendment, filed 24 April 2009, with respect to the rejection of claims 29-42 and 49-56 under 35 USC § 112, first paragraph, for lack of scope of enablement, has been fully considered and is persuasive. The claims have been amended to a method to only inhibit herpes virus. With regards to the lack of scope of enablement for using any of the glycolipids of formula (1) in a method for inhibiting herpes virus, Applicant's argument that the differences among the variables of R^5 is small and that

the original Specification provides sufficient support that a representative number of the instantly claimed glycolipids are shown to inhibit viral activity and activate cytokine activity, is persuasive.

In view of the cancellation of claims 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 and 53, all rejections made with respect to claims 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 and 53 in the previous Office Action are withdrawn.

These rejections have been **withdrawn**.

Claim Objections

Claims 30, 32, 34, 36, 38, 40, 42, 50, 52, 54 and 55 are objected to because of the following informalities: for depending upon a withdrawn claim. Appropriate correction is required.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 24 April 2009, wherein the limitations in pending claims 30, 32, 34, 50, 55 and 56 as amended now have been changed; claims 57-59 depend from claims 50, 55 and 56, respectively. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 24 October 2009, have been modified and are listed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 30, 32, 34, 50 and 55-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over PG Pub No. US 2006/0211856 A1 to Tsuji *et al.* (PTO-892, Ref. A), in view of U.S. Patent No. 5,672,693 to Kawahara (herein referred to as the '693 patent; PTO-892, Ref. B), in view of journal publication by Kawano *et al.* (PTO-892, Ref. U).

Tsuji *et al.* teach compounds represented by the structure of formula (1) as ligands for NKT cells and methods of using the said compounds in modulating immune responses (paragraphs 0008-0018). As indicated by Tsuji *et al.*, an alkyl group refers to a saturated aliphatic hydrocarbon with 1-30 carbon atoms that may be substituted or unsubstituted (paragraph 0164). Thus, the compound of formula (1), wherein the glycosyl residue has the glucose configuration, R is COOH, R_2, R_3 and R_5 is H, R_3' is OH, R_4 is C_{13} alkyl and R_4' is C_{12} alkyl, is the same as the compound used in Applicants' instantly claimed methods. The compound of formula (1) may be a ligand for an NKT cell and therefore stimulates NKT cell activity by contacting an NKT cell with the said compound of formula (1) (paragraphs 0077 and 0079). The compounds of formula (1) may also be used in a method of stimulating or enhancing cytokine production in a subject, the method including administering to the subject any one of the compounds of formula (1), whereby an NKT cell in the subject secretes a cytokine following contact with the compound (paragraph 0089). The secreted cytokines may be IFN-γ or IL-4 (paragraph 0089). The NKT cells may also induce maturation of the dendritic cells, which in turn may promote IL-12 secretion by the dendritic cells (paragraph 0339). Furthermore, enhancement of immunogenicity by administration of the compound/composition comprising the compounds of formula (1) would immunize the

subject to prevent disease, and/or ameliorate the disease, and/or alter disease progression (paragraph 0328). Examples of infectious virus to which stimulation of a protective immune response is desirable, which may be accomplished by administration of the compound of formula (1), include *Herpesviridae* which covers herpes virus and cytomegalovirus (paragraph 0329). Glycolipids of forumula (1) that were synthesized are shown in Fig. 5. The synthesized compounds encompass *Sphingomonas* glycolipids (GSL), compounds (5) and (6), which differ from α-GalCer in the carbohydrate moiety as they contain galactosyluronic acids as the polar head group instead of galactose. However, they are more physiologically relevant as natural ligands for CD1d-mediated NKT-cell activation since they originate from bacteria (paragraph 0389). As shown in Fig. 9, these compounds stimulate IL-2 secretion in 1.2 (Vα14 Vβ8.2 DN3A4) NKT cell hybridomas (paragraph 0389). Additionally, as shown in Fig. 10, the *Sphingomonas* GSLs are reactive to the same population of human Vα24i NKT cells as α-GalCer, showing that these bacterium-derived antigens are also able to activate NKT cells (paragraph 0389).

Although Tsuji *et al.* disclose a genus that encompasses the compound used in Applicants' instantly claimed method, Tsuji *et al.* do not provide examples to show that the disclosed compounds can be used in the methods as instantly claimed by Applicants. Tsuji *et al.* only disclose examples using α-GalCer and *Sphingomonas* GSL compounds (5) and (6). The compound used in the instantly claimed method differs from the *Sphingomonas* GSL compounds exemplified by Tsuji *et al.* at the C-4 hydroxyl

position. Tsuji *et al.* exemplifies a galuronic acid GSL whereas the instantly claimed invention uses a glucuronic acid GSL.

The Kawahara '693 patent teaches the characterization of glycosphingolipids from the Gram-negative species *Sphingomonas*. One such compound, GSL-1, is the same compound as that used in Applicants' instantly claimed invention (column 3).

Kawano *et al.* teach the activation of NKT cells by different glycosylceramides. As shown in Fig. 1, α-GalCer and α-GlcCer, which differ only in the configuration of the 4-hydroxyl group on the carbohydrate, show no functional difference (p. 1627). Thus, the 4-hydroxyl configuration of the sugar seems not to be important in NKT cell activation (p. 1627, column 1, last bridging paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Tsuji *et al.*, concerning compounds of formula (1) as ligands for NKT cells, with the teachings of the Kawahara '693 patent, regarding the characterizations of glycosphingolipids from *Sphingomonas*, with the teachings of Kawano *et al.*, regarding the lack of importance of the 4-hydroxyl configuration in activation of NKT cells. Since Tsuji *et al.* suggest that *Sphingomonas* GSL compounds bearing a galacturonic acid residue are more physiologically relevant as natural ligands for CD1d-mediated NKT-cell activation since they originate from bacteria, and further show that these compounds can activate NKT cells and stimulate IL-2 secretion, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute other known *Sphingomonas* GSL compounds, such as GSL-1 disclosed in the Kawahara '693 patent, with the expectation that the GSL compound disclosed by in the

Kawahara '693 patent would exhibit similar activity to that of the *Sphingomonas* GSL compounds disclosed by Tsuji *et al.* One of ordinary skill in the art would expect this predictable result based on the teaching of Kawano *et al.* that the 4-hydroxyl configuration of the sugar seems not to be important in NKT cell activation.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 30, 32, 34, 50 and 55-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by van Dommelen *et al.* (PTO-892, Ref. V), in view of journal publication by Wu *et al.* (IDS dated 7 August 2006), in view of U.S. Patent No. 5,672,693 to Kawahara (herein referred to as the '693 patent; PTO-892, Ref. B), in view of journal publication by Kawano *et al.* (PTO-892, Ref. U).

Van Dommelen *et al.* teach that the activation of NKT cells by α-GalCer during murine cytomegalovirus infection resulted in reduced viral replication (abstract; p. 1881, column 1, subheading "Discussion"). Furthermore, the α-GalCer-induced antiviral response was dependent upon both perforin-mediated cytotoxicity and IFN-γ release (p. 1882, column 2). Thus, activated NKT cells are key mediators of the antiviral effects of α-GalCer, with NK cells, IFN-γ and perforin all playing crucial roles (p. 1883, column 1, paragraph 1).

The teachings of van Dommelen *et al.* differ from that of the instantly claimed invention in that α-GalCer is used instead of a gluronic acid glycolipid.

Wu *et al.* teach bacterial glycolipids and analogs as antigens for CD1d-restricted NKT cells. α-GalCer, a lipid found in marine sponge, when bound to CD1d, stimulates rapid Th1 (such as IFN-γ) and Th2 (such as IL-4) cytokine production by NKT cells in mice and human (p. 1351, column 1, bridging paragraph; Figure 1). The glycolipids shown in figure 2 were also tested for their ability to stimulate mouse and human natural killer T (NKT) cells. Compounds 1 and 2 represent *Sphingomonas* bacterial glycolipids that are structurally similar to α-GalCer, but differ mainly in the acidic group present on the carbohydrate (p. 1352, column 1, first incomplete paragraph). These structures may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria (p. 1352, column 1, first incomplete paragraph), as compared to marine sponge. Stimulation of the NKT cell line by the glycolipid compounds resulted in significant IFN-γ and IL-4 secretion, when compared to the negative control (p. 1355, column 2, last paragraph). In addition to stimulating NKT cells, flow cytometric analyses indicated that the receptor of NKT cells also bind to the various glycolipid antigen structures (p. 1356, column 1, first complete paragraph). Since the *Sphingomonas* glycolipids were reactive to the same population of human NKT cells as α-GalCer, Wu *et al.* concluded that this indicates that bacterium-derived antigens are also able to activate NKT cells (p. 1356, column 2, subheading "Conclusion", paragraph 2). Furthermore, they were able to demonstrate responses to the *Sphingomonas* compounds *in vivo*, and mice deficient for NKT cells have a reduced ability to clear bacteria from the liver (p. 1356, column 2, subheading "Conclusion", paragraph 1).

The teachings of the Kawahara '693 patent and Kawano *et al.* were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of van Dommelen *et al.*, concerning the reduction of viral replication when NKT cells are activated by α-GalCer during murine cytomegalovirus infection, with the teachings of Wu *et al.*, regarding the effect of various glycolipids, including *Sphingomonas* bacterial glycolipids, in activating NKT cells and cytokine production, with the teachings of the Kawahara '693 patent, regarding the characterizations of glycosphingolipids from *Sphingomonas*, with the teachings of Kawano *et al.*, regarding the lack of importance of the 4-hydroxyl configuration in activation of NKT cells. Since van Dommelen *et al.* teach that α-GalCer can activate NKT cells, thereby inhibiting cytomegalovirus replication, and Wu *et al.* teach that α-GalCer analogs wherein lipids varying in chain lengths still have significant activities toward NKT cell activation and that the *Sphingomonas* bacterial glycolipids carrying the acidic group may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria and not marine sponge (origination of α-GalCer), and the Kawahara '693 patent teaches various structures of glycolipids from the bacteria *Sphingomonas*, one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Wu *et al.*, that the structures from *Sphingomonas paucimobilis* may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria (p. 1352, column 1). Thus, as viruses are infectious agents are

more similar to bacteria than marine sponge, these compounds may also be more physiologically relevant in inhibiting cytomegalovirus replication. Furthermore, since Kawano *et al.* taught that the 4-hydroxyl configuration of the sugar seems not to be important in NKT cell activation, one of ordinary skill in the art would know that this structural component of the glycolipid does not play a significant role in NKT cell activation, and thus the GSL-1 compound taught in the Kawahara '693 patent would be expected to have similar activity to the *Sphingomonas* GSL compounds taught by Wu *et al.*

With regards to administration of the compound to a mammal, Applicants are requested to note that the courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. See MPEP § 2107.01.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claims 30, 32, 34, 40, 42 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Kakimi *et al.* (of record), in view of journal publication by Wu *et al.* (IDS dated 7 August 2006) and journal publication by Wiese *et al.* (of record), as evidenced by Trinchieri *et al.* (of record).

Kakimi *et al.* teach that natural killer T (NKT) cell activation by α-galactosylceramide (α-GalCer) inhibits hepatitis B virus replication *in vivo*. The antiviral effect of α-GalCer is rapid and specific, and is associated with the induction of IFN-γ and IFN-α/β in the liver (p. 927, column 1, subheading "Discussion"). Since the induction of IFN-γ and IFN-α/β as well as the inhibition of HBV replication occur before a significant number of inflammatory cells are recruited into the organ, it is likely that these cytokines are produced by cells that reside in the liver, specifically NKT cells that are known to produce IFN-γ very rapidly in response to α-GalCer and NK cells that are promptly activated by NKT cells and enhance induction of IFN-γ production (p. 927, column 2, bridging paragraph). Based on the results of their study, Kakimi *et al.* conclude that α-GalCer inhibits HBV replication by directly activating NKT cells and by secondarily activating NK cells to secrete antiviral cytokines in the liver (p. 921, abstract).

Kakimi *et al.* do not explicitly teach activation of NKT cells, NK cells and inhibition of HBV by the compound of formula (3) wherein R^6 is H and R^{51} is as shown in instant claim 28.

Wu *et al.* teach bacterial glycolipids and analogs as antigens for CD1d-restricted NKT cells. α-GalCer, a lipid found in marine sponge, when bound to CD1d, stimulates rapid Th1 (such as IFN-γ) and Th2 (such as IL-4) cytokine production by NKT cells in mice and human (p. 1351, column 1, bridging paragraph; Figure 1). The glycolipids shown in figure 2 were also tested for their ability to stimulate mouse and human natural killer T (NKT) cells. Compounds 1 and 2 represent *Sphingomonas* bacterial glycolipids

that are structurally similar to α-GalCer, but differ mainly in the acidic group present on the carbohydrate (p. 1352, column 1, first incomplete paragraph). These structures may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria (p. 1352, column 1, first incomplete paragraph), as compared to marine sponge. Stimulation of the NKT cell line by the glycolipid compounds resulted in significant IFN-γ and IL-4 secretion, when compared to the negative control (p. 1355, paragraph 2, last paragraph). In addition to stimulating NKT cells, flow cytometric analyses indicated that the receptor of NKT cells also bind to the various glycolipid antigen structures (p. 1356, column 1, first complete paragraph). Since the *Sphingomonas* glycolipids were reactive to the same population of human NKT cells as α-GalCer, Wu *et al.* concluded that this indicates that bacterium-derived antigens are also able to activate NKT cells (p. 1356, column 2, subheading "Conclusion", paragraph 2). Furthermore, they were able to demonstrate responses to the *Sphingomonas* compounds *in vivo*, and mice deficient for NKT cells have a reduced ability to clear bacteria from the liver (p. 1356, column 2, subheading "Conclusion", paragraph 1).

Wiese *et al.* teach the characterization of some physiochemical properties of the monosaccharide-type fraction of glycosphingolipids from the outer leaflet of the Gram-negative species *Sphingomonas paucimobilis*. Its structure is shown in Figure 1, indicating it has two variants for the R group (p. 322).

It is noted that the references do not explicitly teach a method of accelerating IL-10 and IL-6 production which comprises administering the cell activator to a mammal.

However, Wu *et al.* explicitly teach that α-GalCer, when bound to CD1d, stimulates rapid Th1 and Th2 cytokine production by NKT cells in mice and human (p. 1351, column 1, bridging paragraph; Figure 1). As evidenced by Trinchieri *et al.* (of record), Th2 cytokine production includes IL-4, IL-5, IL-6 and IL-10 (p. 123, column 1, first paragraph).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kakimi *et al.*, concerning the inhibition of hepatitis B replication by the activation of NKT cells by α-GalCer, with the teachings of Wu *et al.*, regarding the effect of various glycolipids, including *Sphingomonas* bacterial glycolipids, in activating NKT cells and cytokine production, with the teachings of Weise *et al.*, regarding the physiochemical properties of glycolipids from the bacteria *Sphingomonas paucimobilis*. Since Kakimi *et al.* teach that α-GalCer can activate NKT cells and NK cells, thereby inhibiting hepatitis B replication, and Wu *et al.* teach that α-GalCer analogs wherein lipids varying in chain lengths still have significant activities toward NKT cell activation and that the *Sphingomonas* bacterial glycolipids carrying the acidic group may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria and not marine sponge (origination of α-GalCer), and Weise *et al.* teach various structures of glycolipids from the bacteria *Sphingomonas paucimobilis*, one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Wu *et al.*, that the structures from *Sphingomonas paucimobilis* may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from

bacteria (p. 1352, column 1). Thus, as viruses are infectious agents are more similar to bacteria than marine sponge, these compounds may also be more physiologically relevant in inhibiting hepatitis B replication. Furthermore, since Wu *et al.* indicated that glycolipids with varying chain lengths still have significant activities toward NKT cell activation, one of ordinary skill in the art would know that this structural component of the glycolipid does not play a significant role in NKT cell activation.

With regards to administration of the compound to a mammal, Applicants are requested to note that the courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. See MPEP § 2107.01.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0004]

Claims 30, 32, 34, 36, 38, 40 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Kitamura *et al.* (of record), in view of journal publication by Wu *et al.* (IDS dated 7 August 2006) and journal publication by Wiese *et al.* (of record).

Kitamura *et al.* teach the NKT cell ligand, α-GalCer, demonstrates its immunopotentiating effect by inducing IL-12 production by dendritic cells and IL-12 receptor expression on NKT cells. As shown in Figure 3, Kitamura *et al.* demonstrated

that α-GalCer upregulates IL-12 R expression *in vivo* and this upregulation is blocked by mAbs against Il-12 or IFN-γ (p. 1125, column 2, last paragraph). Based on the results of their experiments, Kitamura *et al.* speculate that the following series of events is induced upon culture of α-GalCer with dendritic cells and NKT cells: (a) α-GalCer first binds to CD1d molecules on dendritic cells; (b) NKT cells recognize α-GalCer-bound dendritic cells via their TCRs and also interact with dendritic cells via CD40/CD40L; (c) during this interaction, the dendritic cells produce IL-12; (d) the endogenously produced IL-12 stimulates IFN-γ production by NKT cells; and (e) IFN-γ produced by NKT cells upregulates IL-12R on NKT cells in an autocrine manner.

Kitamura *et al.* do not explicitly teach activation of NKT cells, acceleration of cytokines and activation of dendritic cells by the compound of formula (3) wherein R^6 is H and R^{51} is as shown in instant claim 28.

The teachings of Wu *et al.* and Wiese *et al.* were as described above in section [0003] of the claim rejections under 35 USC § 103.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kitamura *et al.*, concerning the immunopotentiating effect of α-GalCer in inducing IL-12 production by dendritic cells, with the teachings of Wu *et al.*, regarding the effect of various glycolipids, including *Sphingomonas* bacterial glycolipids, in activating NKT cells and cytokine production, with the teachings of Weise *et al.*, regarding the physiochemical properties of glycolipids from the bacteria *Sphingomonas paucimobilis*. Since Kitamura *et al.* teach that α-GalCer upregulates IL-12 production by activating dendritic cells, and Wu *et al.* teach

that α-GalCer analogs wherein lipids varying in chain lengths still have significant activities toward NKT cell activation and that the *Sphingomonas* bacterial glycolipids carrying the acidic group may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria and not marine sponge (origination of α-GalCer), and Weise *et al.* teach various structures of glycolipids from the bacteria *Sphingomonas paucimobilis,* one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Wu *et al.*, that the structures from *Sphingomonas paucimobilis* may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria (p. 1352, column 1). Since Wu *et al.* indicated that glycolipids with varying chain lengths still have significant activities toward NKT cell activation, one of ordinary skill in the art would know that this structural component of the glycolipid does not play a significant role in NKT cell activation, and thus can use a large array of glycolipids for NKT cell and NK cell activation and cytokine acceleration.

With regards to administration of the compound to a mammal, Applicants are requested to note that the courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. See MPEP § 2107.01.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0005]

Claims 50 and 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Tay *et al.* (of record), in view of journal publication by Kakimi *et al.* (of record), journal publication by Wu *et al.* (IDS dated 7 August 2006), and journal publication by Wiese *et al.* (of record).

Tay *et al.* teach that the antiviral effector mechanisms by which NK cells control murine cytomegalovirus (MCMV) infection in the liver are abrogated by *in vivo* administration of L-NMMA, a competitive inhibitor of NOS (nitric oxide synthase). Treating mice with L-NNMA enhanced MCMV titers in the liver (p. 272, bridging paragraph; p. 273, column 2, first full paragraph). This data adds to the evidence that one of the ways IFN-γ can exert its antiviral actions is through the induction of NOS to produce nitric oxide (p. 273, column 2, first full paragraph).

Tay *et al.* do not explicitly teach a method wherein NO production is accelerated by the compound of formula (3) wherein R^6 is H and R^{51} is as shown in instant claim 28, nor Tay *et al.* explicitly teach a method of inhibiting herpesvirus activity by administration of the said compound of formula (3).

The teachings of Kakimi *et al.*, Wu *et al.*, and Wiese *et al.* were as described above in section [0003] of the claim rejections under 35 USC § 103.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Tay *et al.*, concerning the induction of NO production by NK cells and IFN-γ in murine cytomegalovirus infection, with the teachings of Kakimi *et al.*, regarding the inhibition of hepatitis B replication (cytomegalovirus) by

the activation of NKT cells and NK cells by α-GalCer, with the teachings of Wu *et al.*, regarding the effect of various glycolipids, including bacterial glycolipids, in activating NKT cells and cytokine production, with the teachings of Weise *et al.*, regarding the physiochemical properties of glycolipids from the bacteria *Sphingomonas paucimobilis*. Since Kakimi *et al.* teach that α-GalCer can activate NKT cells and NK cells, thereby inhibiting hepatitis B replication, Tay *et al.* teach that NO production is effected by IFN-γ, and Wu *et al.* teach that α-GalCer analogs wherein lipids varying in chain lengths still have significant activities toward NKT cell activation and that the *Sphingomonas* bacterial glycolipids carrying the acidic group may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria and not marine sponge (origination of α-GalCer), and Weise *et al.* teach various structures of glycolipids from the bacteria *Sphingomonas paucimobilis*, one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Wu *et al.*, that the structures from *Sphingomonas paucimobilis* may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria (p. 1352, column 1). Since Wu *et al.* indicated that glycolipids with varying chain lengths still have significant activities toward NKT cell activation, one of ordinary skill in the art would know that this structural component of the glycolipid does not play a significant role in NKT cell activation.

With regards to administration of the compound to a mammal, Applicants are requested to note that the courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical

product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. See MPEP § 2107.01.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 24 April 2009 with respect to the rejection of claims 30, 32, 34, 40, 42, 50, 52, 55 and 56 made under 35 USC § 103(a) as being unpatentable over Kakimi *et al.*, in view of Wu *et al.* and Wiese *et al.*, the rejection of claims 30, 32, 34, 36, 38, 40, 51 and 52 made under 35 USC § 103(a) as being unpatentable over Kitamura *et al.*, in view of Wu *et al.* and Wiese *et al.*, and the rejection of claims 54 made under 35 USC § 103(a) as being unpatentable over Tay *et al.* in view of Kakimi *et al.*, in view of Wu *et al.* and Wiese *et al.*, have been fully considered but they are not persuasive.

Applicants argue that Wu *et al.* explicitly disclose that the GSL of formula (3) has IFN-γ and IL-4 production activity that is much smaller than those of α-GalCer and thus one would have no motivation to select the GSL with lower activity to achieve the instantly claimed invention. This argument is not persuasive because one would not be merely choosing the GSL disclosed by Wu *et al.* and modifying it to achieve the instantly claimed invention. Rather, based on the Wu *et al.* teaching that these structures may be more physiologically relevant as natural ligands for CD1d-mediated NKT cell activation because they originate from bacteria, one would have been motivated to look

at other *Sphingomonas* structures to see if they show different and better activity from those tested by Wu *et al.*

Applicants additionally argue that Wiese *et al.* disclose that GSL acts as an activator of complement and Wu *et al.* teach that GSL does not directly affect a cell, but rather, only indirectly acts on the cell, which is contrary to the instantly claimed invention wherein GSL directly affects the cell. This argument is not persuasive because Kakimi *et al.* Specifically teach that α-GalCer directly activates NKT cells. Applicants are requested to note that the recitation of the claims do not distinguish whether the GSL acts directly on the cell or indirectly. The recitation of the claims merely requires that GSL stimulates various cells and cytokines by administration of the GSL compound without regards to it being direct or indirect. Moreover, even if the recitation of the claims were drawn to direct activation by the compound, how the various cells or cytokines are activated is considered a mere mechanism of action of the GSL. Applicant's recitation of a new mechanism of action for the prior art method would not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps. Note that a mechanism of action of a treatment would not by itself carry patentable weight if the prior art teaches the same or nearly the same method steps.

Applicants further argue that although a certain compound has immunopharmacological activity, it is difficult to determine if that compound has other specific immunopharmacological activities, and further cite the teachings of Homma *et al.* to substantiate their argument. Applicants also argue that based on the teachings of

Homme *et al.*, in order to find that a certain chemical compound has a certain immunopharmacological activity, the skilled person has to carry out quite a lot of experiments. These arguments are not persuasive because the compounds tested by Homma *et al.* are lipid A and lipid A analogs which may function differently from GalCer and GSL compounds. Furthermore, the teachings of Kakimi *et al.*, Kitamura *et al.*, Tay *et al.* and Wu *et al.* specifically teach that α-GalCer plays a role in the stimulation of the indicated cells and cytokines, and Wu *et al.* also teach that *Sphingomonas* GSLs are reactive to the same population of human NKT cells as α-GalCer. Thus, as α-GalCer is more closely related to the *Sphingomonas* GSL compounds and the prior art explicitly teaches that these compounds are involved in the activation and stimulation of NKT cells and various cytokines, Applicants' argument that the cytokines and their antiviral activity may have less relationship to each other based on the teachings of Homme *et al.*, which is related to lipid A, a structure that is less similar to α-GalCer, is insufficient to rebut the *prima facie* case herein.

Applicants' results as disclosed in the instant Specification have been reviewed and are not considered to be unexpected in view of the teachings of the prior art.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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